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(71) Applicant *(for all designated States except US)*: **BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH** [DE/DE]; Patentabteilung, Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

(72) Inventors *(for all designated States except CA, US)*: **BÄR, Thomas**; Berggässle 5, 78479 Reichenau (DE). **STADLWIESER, Josef**; Im Apfelgarten 3, 78465 Konstanz (DE). **ULRICH, Wolf-Rüdiger**; Hebelstrasse 3, 78464 Konstanz (DE). **DOMINIK, Andreas**; Engelbert-Weltin-Weg 1, 78476 Allenbach (DE). **BUNDSCHUH, Daniela**; Rheingutstrasse 17, 78462 Konstanz (DE). **ZECH, Karl**; Am Guckenbühl 17, 78465 Konstanz (DE). **SOMMERHOFF, Christian**; Thomassstrasse 7, 81929 München (DE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **MARTIN, Thomas** [DE/DE]; St.-Martins-Weg 13, 78462 Konstanz (DE).

(74) Common Representative: **BYK GULDEN LOMBERG CHEMISCHE FABRIK GMBH**; Patentabteilung, Byk-Gulden-Strasse 2, 78467 Konstanz (DE).

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(54) Title: TRYPTASE INHIBITORS

(57) Abstract: Compounds of the formula (I), in which M, A1, A2, K1 and K2 have the meanings indicated in the description are novel active tryptase inhibitors.

Tryptase inhibitors

Field of application of the invention

The invention relates to novel tryptase inhibitors which are used in the pharmaceutical industry for preparing medicaments.

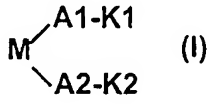
Known technical background

The international applications WO95/32945, WO96/09297, WO98/04537, WO99/12918, WO99/24395, WO99/24407 and WO99/40073 describe low-molecular-weight bivalent compounds for use as tryptase inhibitors.

Description of the invention

It has now been found that the compounds of the formula I, which are described in more detail below, have surprising and particularly advantageous properties.

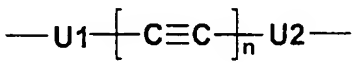
The invention provides compounds of the formula I



(I)

in which

M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [-CH_2-], ethylene [-CH_2-CH_2-], trimethylene [-CH_2-CH_2-CH_2-], tetramethylene [-CH_2-CH_2-CH_2-CH_2-] or isopropylidene [-$C(CH_3)_2$-],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -C(O)-, -O-C(O)-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH-, -O-C(O)-O-, $-O-(CH_2)_r-C(O)-$, $-O-(CH_2)_m-O-C(O)-$ or $-O-(CH_2)_m-NH-C(O)-$,

r is 1, 2, 3 or 4,

m is 1, 2, 3 or 4,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH- or -O-C(O)-O-,

B1 and B2 are identical or different and are 1-4C-alkylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,4-phenylene, 1,3-phenylene, 1,4-piperazinylene or 1,4-piperidinylene,

K1 is -B3-X1, -B3-Y1 or -B3-Z1-B5-X1,

K2 is -B4-X2, -B4-Y2 or -B4-Z2-B6-X2,

B3 and B4 are identical or different and are a bond or 1-4C-alkylene,

B5 and B6 are identical or different and are a bond or 1-2C-alkylene,

X1 and X2 are identical or different and are amino, aminocarbonyl or amidino,

Y1 and Y2 are imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1, B2, B3, B4, Z1, Z2, X1 or X2, there would be a direct linkage of two heteroatoms.

1-4C-alkylene represents straight-chain or branched 1-4C-alkylene radicals, for example the methylene [$-CH_2-$], ethylene [$-CH_2-CH_2-$], trimethylene [$-CH_2-CH_2-CH_2-$], tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$], 1,2-dimethylethylene [$-CH(CH_3)-CH(CH_3)-$], 1,1-dimethylethylene [$-C(CH_3)_2-CH_2-$], 2,2-dimethylethylene [$-CH_2-C(CH_3)_2-$], isopropylidene [$-C(CH_3)_2-$] or the 1-methylethylene [$-CH(CH_3)-CH_2-$] radicals.

By definition, the groups Z1 and Z2 are located between groups B3 and B5 (-B3-Z1-B5-) and B4 and B6 (-B4-Z2-B6-), respectively. Accordingly, in the divalent groupings mentioned by way of example (for example 3,6-indolylene), the first number indicates the point of attachment to the group B3 and B4, respectively, and the second number indicates the point of attachment to the group B5 and B6, respectively.

In the context of this application, the term "terminal nitrogen atom" means in each case a nitrogen atom in the groups designated X1, X2, Y1 and Y2.

If the group X1 or X2 contains only one nitrogen atom, this nitrogen atom is the terminal nitrogen atom.

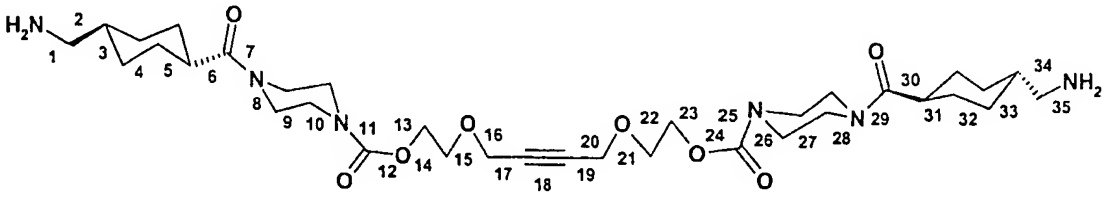
If the group X1 or X2 contains a plurality of nitrogen atoms, the nitrogen atom which is furthest from the atom by means of which the bond to the group B3 (B5) or B4 (B6) is established is the terminal nitrogen atom.

If the group Y1 or Y2 contains only one ring nitrogen atom, this ring nitrogen atom is the terminal nitrogen atom.

If the group Y1 or Y2 contains a plurality of ring nitrogen atoms, the ring nitrogen atom which is furthest from the atom by means of which the bond to the group B3 or B4 is established is the terminal nitrogen atom.

According to the invention, the direct route between the nitrogen atoms which act as terminal nitrogen atoms in the groups defined as X1 (Y1) or X2 (Y2) is considered to be the number of bonds which is obtained by counting the bonds which represent the shortest possible connection between the terminal nitrogen atoms.

The following example is meant to illustrate the determination of the number of bonds on the direct route between two terminal nitrogen atoms:



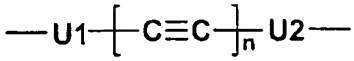
Here, the direct route comprises 35 bonds.

Suitable salts for compounds of the formula I are all acid addition salts. Particular mention may be made of the pharmaceutically acceptable salts of inorganic and organic acids customarily used in pharmacy. Those suitable are water-soluble and water-insoluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulfuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulfosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulfonic acid, methanesulfonic acid or 3-hydroxy-2-naphthoic acid, where the salts are employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically unacceptable salts which can be obtained initially as process products, for example in the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically acceptable salts by processes known to the person skilled in the art.

It is known to the person skilled in the art that the compounds according to the invention, and also their salts, may contain varying amounts of solvents, for example when they are isolated in crystalline form. The invention therefore also embraces all solvates and in particular all hydrates of the compounds of the formula I, and also all solvates and in particular all hydrates of the salts of the compounds of the formula I.

Compounds of the formula I which are to be emphasized are those in which
M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [$-CH_2-$], ethylene [$-CH_2-CH_2-$], trimethylene [$-CH_2-CH_2-CH_2-$], tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$] or isopropylidene [$-C(CH_3)_2-$],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -O-C(O)-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH-, -O-C(O)-O-, $-O-(CH_2)_r-C(O)-$, $-O-(CH_2)_m-O-C(O)-$ or $-O-(CH_2)_m-NH-C(O)-$,

r is 1 or 2,

m is 2,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,

B1 and B2 are identical or different and are 1-4C-alkylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,4-phenylene, 1,3-phenylene, 1,4-piperazinylene or 1,4-piperidinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical or different and are a bond or 1-2C-alkylene,

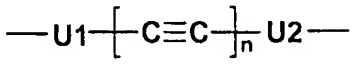
B5 and B6 are identical or different and are a bond or 1-2C-alkylene,

X1 and X2 are identical or different and are amino or amidino,

Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

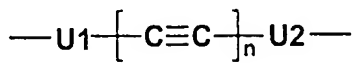
and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

Compounds of the formula I which are to be particularly emphasized are those in which
M is a central building block of the formula below



n is 1 or 2,
U1 and U2 are identical or different and are methylene [$-CH_2-$], tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$] or isopropylidene [$-C(CH_3)_2-$],
A1 is -A3-B1-A5-,
A2 is -A4-B2-A6-,
A3 and A4 are identical or different and are -O-C(O)-, -O-C(O)-NH- or $-O-(CH_2)_m-O-C(O)-$,
m is 2,
A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,
B1 and B2 are identical or different and are ethylene or 1,4-piperazinylene,
K1 is -B3-Z1-B5-X1,
K2 is -B4-Z2-B6-X2,
B3 and B4 are identical or different and are a bond or methylene,
B5 and B6 are identical and are methylene,
X1 and X2 are identical and are amino,
Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,
and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

An embodiment of the compounds of the formula I which are to be particularly emphasized are those in which
M is a central building block of the formula below



n is 1 or 2,
U1 and U2 are identical or different and are methylene [$-CH_2-$] or isopropylidene [$-C(CH_3)_2-$],
A1 is -A3-B1-A5-,
A2 is -A4-B2-A6-,
A3 and A4 are identical or different and are -O-C(O)-, -O-C(O)-NH- or $-O-(CH_2)_m-O-C(O)-$,
m is 2,
A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,

B1 and B2 are identical or different and are ethylene or 1,4-piperazinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical and are a bond or methylene,

B5 and B6 are identical and are methylene,

X1 and X2 are identical and are amino,

Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

Preferred compounds of the formula I of the above embodiment are

1,4-bis-[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,

1,4-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,

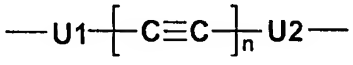
1,4-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne, and

1,6-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne,

and the salts of these compounds, their N-oxides and the salts thereof.

Further preferred compounds of the formula I are those in which

M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical and are methylene [$-CH_2-$]

or tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical and are -O-C(O)- or $-O-(CH_2)_m-O-C(O)-$,

m is 2,

A5 and A6 are identical and are -C(O)- or -C(O)-NH-,

B1 and B2 are identical and are 1,4-piperazinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical and are a bond or methylene,

B5 and B6 are identical and are methylene,

X1 and X2 are identical and are amino,

Z1 and Z2 are identical and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds.

Especially preferred compounds of the formula I are
1,4-bis-[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,4-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,4-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,6-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne,
1,12-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne,
1,12-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne, and
1,6-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne,
and the salts of these compounds.

The compounds of the formula I are constructed from a large number of building blocks (M, A1, A2, A3, A4, A5, A6, B1, B2, B3, B4, B5, B6, X1, X2, Y1, Y2, Z1 and Z2). In principle, they can be synthesized starting with any of these building blocks. If the compounds of the formula I are constructed largely symmetrically, it is favorable to start the synthesis with the central building block M, whereas in the case of predominantly asymmetrical compounds of the formula I a synthesis starting with one of the end groups K1 or K2 may be advantageous.

Suitable starting materials for synthesizing the compounds of the formula I according to the invention are, for example, 2-butyne-1,4-diol, 2,4-hexadiyne-1,6-diol, 2,5-dimethyl-3-hexyne-2,5-diol, 2,7-dimethyl-3,5-octadiyne-2,7-diol or dodec-5,7-diyne-1,12-diol.

Here, the building blocks are linked using always the same pattern, known per se to the person skilled in the art.

It is known to the person skilled in the art that the compounds of the formula I can either be synthesized building block by building block, or by initially constructing relatively large fragments consisting of several individual building blocks, which can then be joined to give the complete molecule.

Owing to the meanings which the individual building blocks of the compounds of the formula I can assume, ether [-O-], ester [-O-C(O)-], keto [-C(O)-], amide [-C(O)-NH-, -NH-C(O)-], carbamate [-NH-C(O)-O-, -O-C(O)-NH-], carbamide [-NH-C(O)-NH-] or carbonate [-O-C(O)-O-] bridges are present in the compounds of the formula I.

How to prepare such bridges is known per se to the person skilled in the art; suitable methods and starting materials for their preparation are described, for example, in March, Advanced Organic Chemistry, Reactions, Mechanisms and Structure, Third Edition, 1985, John Wiley & Sons.

Ether bridges can be prepared, for example, by the method of Williamson.

There is a large number of known methods for preparing ester bridges. An example which may be mentioned here is the reaction of acids with alcohols, preferably using H_2SO_4 or p-toluenesulfonic acid as catalyst; or with addition of a dehydrating agent, such as, for example, molecular sieve or a carbodiimide. Furthermore, the reaction of acyl chlorides with alcohols may be mentioned here.

Keto bridges can be introduced, for example, as a component of relatively large building blocks, such as, for example, carboxylic acid derivatives.

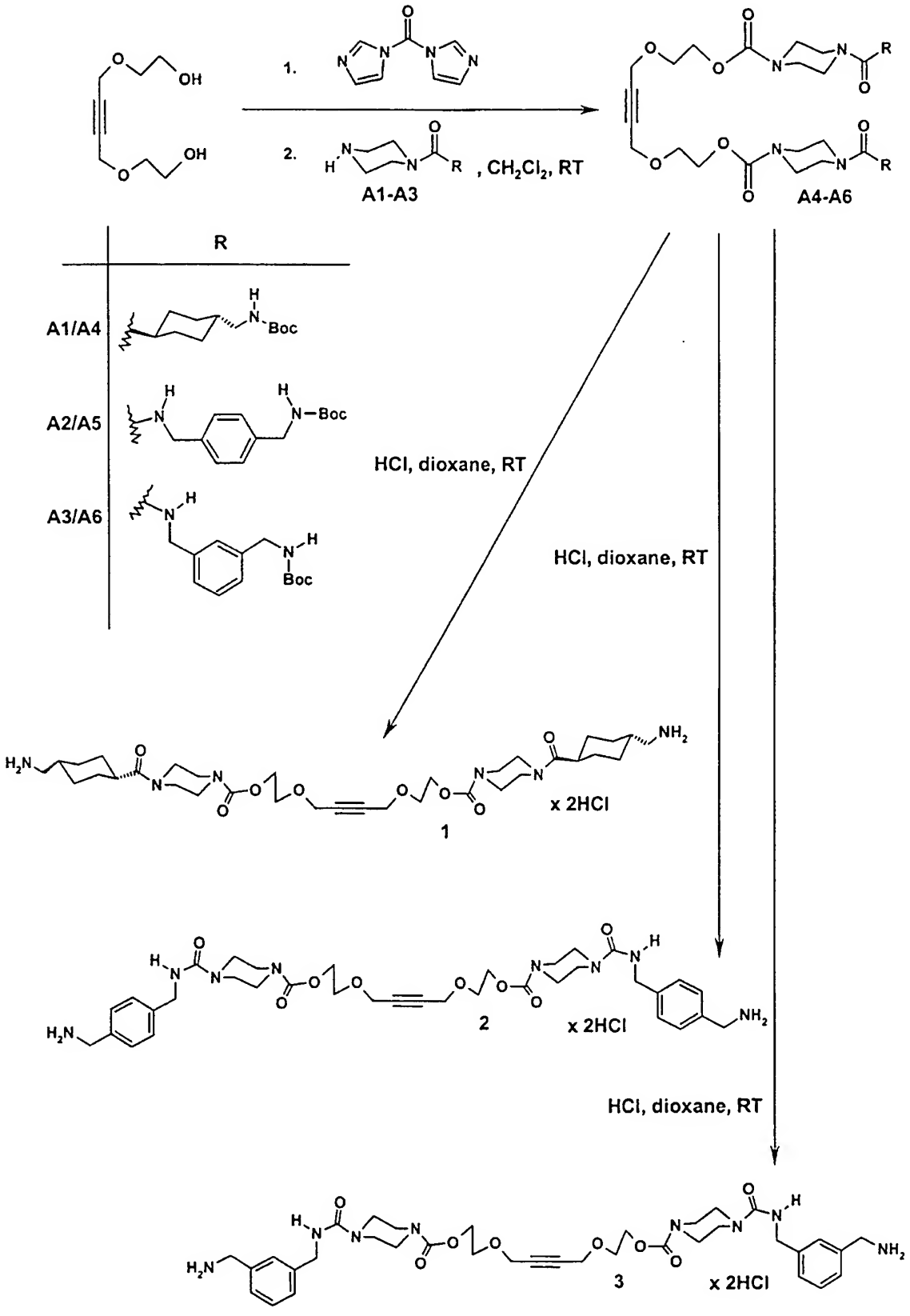
There is also a large number of known methods for preparing amide bridges. An example which may be mentioned here is the reaction of acyl chlorides with primary or secondary amines. Furthermore, reference is also made to all the methods which have been developed for peptide chemistry.

Carbamate bridges can be prepared, for example, by reacting chloroformates with amines. The chloroformates for their part can be synthesized from alcohols and phosgene. A further variant for constructing carbamate bridges is the addition of alcohols to isocyanates. Similarly to carbamate bridges, it is possible to prepare carbonate bridges starting from chloroformates, by reaction with alcohols (instead of amines).

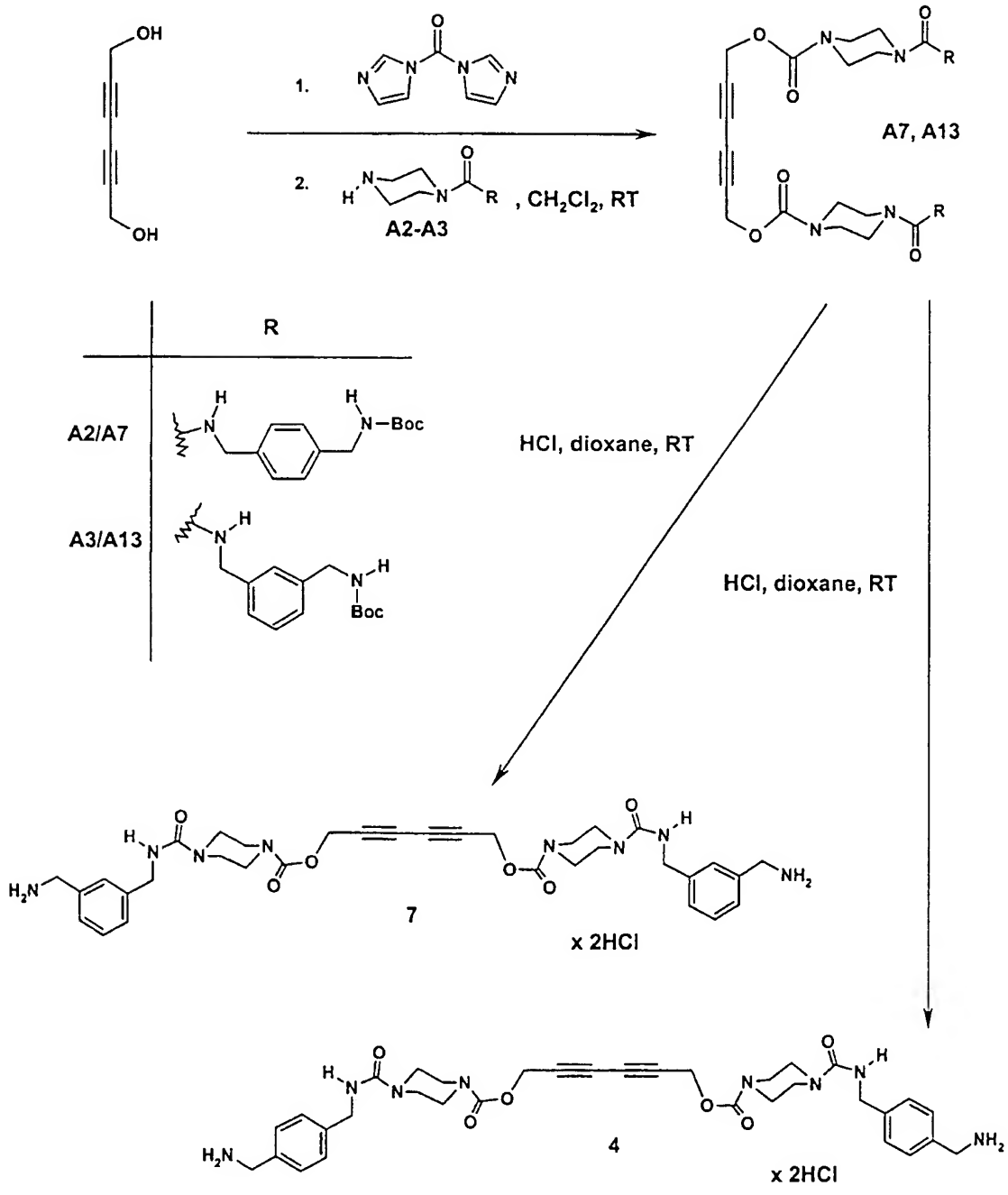
Carbamide bridges can be prepared, for example, by reacting isocyanates with amines.

The preparation of compounds of the formula I may be shown in an exemplary manner using the reaction schemes below. Reaction scheme 1 shows the preparation of the exemplary compounds 1, 2 and 3. Reaction scheme 2 shows the preparation of the exemplary compounds 4 and 7. Reaction scheme 3 shows the preparation of the exemplary compounds 5 and 6. Other compounds of the formula I can be prepared analogously, or by using the abovementioned methods known per se to the person skilled in the art.

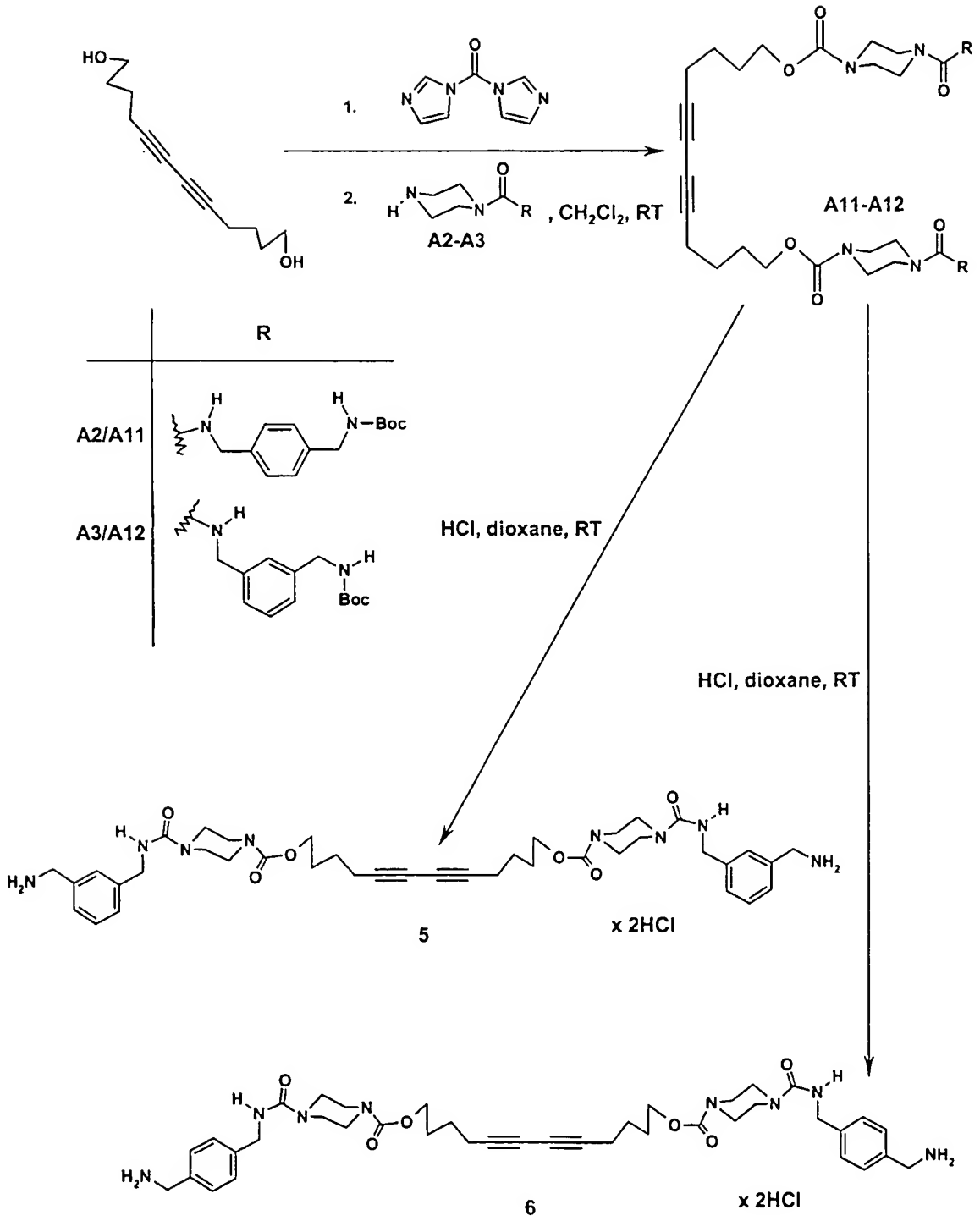
Reaction scheme 1:



Reaction scheme 2:



Reaktion scheme 3:



It is also possible to convert compounds of the formula I by derivatization into other compounds of the formula I. Thus, for example, compounds of the formula I having a nitrogen-containing heteroaryl, heteroarylene, heterocycloalkyl or heterocycloalkylene building block can be converted by oxidation into the corresponding N-oxides.

The N-oxidation is carried out in a manner which is likewise known to the person skilled in the art, for example using hydrogen peroxide in methanol or m-chloroperoxybenzoic acid in dichloromethane at room temperature. Which reaction conditions are required in the particular case for carrying out the process is known to the person skilled in the art owing to his expert knowledge.

It is furthermore known to the person skilled in the art that if there are a number of reactive centers on a starting material or intermediate, it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description of the use of a large number of proven protective groups is found, for example, in T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1991.

The isolation and purification of the substances according to the invention is carried out in a manner known per se, for example by distilling off the solvent under reduced pressure and recrystallizing the resulting residue from a suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on a suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (for example a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low-molecular-weight aliphatic alcohol, such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically unacceptable salts can be converted into pharmacologically acceptable salts.

The examples below serve to illustrate the invention in more detail without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

In the examples below, the abbreviation RT stands for room temperature, h for hours, min. for minutes, m. p. for melting point, EDC for N'-(3-dimethylaminopropyl)-N-ethylcarbodiimide and HOBT for 1-hydroxy-1H-benzotriazole, TLC stands for thin-layer chromatography and MS for mass spectrometry. The compounds mentioned by way of example and their salts are the preferred subject of the invention.

Examples

End products:

General procedure

A solution of the Boc-protected divalent compound (A4 – A7, A11 – A13; 1.0 mmol) in question in dioxane (4 ml) is admixed with a saturated solution of HCl in dioxane (4 ml, 18.0 mmol) and stirred at RT for 4 h. The resulting precipitate is filtered off under an N_2 atmosphere and washed first with dioxane (2 x 5 ml) and then with diethyl ether (3 x 5 ml). Drying under reduced pressure gives the title compounds (end products 1-7) as colorless solids.

1. **1,4-Bis-[4-(*trans*-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne dihydrochloride**

MS: calc.: $C_{34}H_{56}N_6O_8$ (676.3), found: $[MH^+]$ 677.3

2. **1,4-Bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne dihydrochloride**

MS: calc.: $C_{38}H_{50}N_8O_8$ (722.2), found: $[MH^+]$ 723.2

3. **1,4-Bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne dihydrochloride**

MS: calc.: $C_{36}H_{50}N_8O_8$ (722.2), found: $[MH^+]$ 723.2

4. **1,6-Bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne dihydrochloride**

MS: calc.: $C_{34}H_{42}N_8O_6$ (658.1), found: $[MH^+]$ 659.1

5. **1,12-Bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne dihydrochloride**

MS: calc.: $C_{40}H_{54}N_8O_6$ (742.2), found: $[MH^+]$ 743.2

6. **1,12-Bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne dihydrochloride**

MS: calc.: $C_{40}H_{54}N_8O_6$ (742.2), found: [MH^+] 743.2

7. **1,6-Bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne dihydrochloride**

MS: calc.: $C_{34}H_{42}N_8O_6$ (658.1), found: [MH^+] 659.1

Starting materials:

A1. Trans-4-N-*tert*-butoxycarbonylaminomethylcyclohexylcarbonyl-1-piperazine

At RT, benzyl 4-{1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexyl]carbonyl}piperazine-1-carboxylate (starting material A8, 0.4 g, 0.87 mmol) is dissolved in MeOH (20 ml) and admixed with palladium-on-carbon (10% Pd, 0.2 g). Under an atmosphere of hydrogen and at RT, the mixture is stirred in a circulation hydrogenation apparatus for 3 h. After uniform conversion (TLC), the catalyst is filtered off and the solution is concentrated under reduced pressure. This gives the title compound (0.28 g) as a colorless solid. Without any further purification, the compound could be used for the next step. TLC, silica gel, glass plates, [CH_2Cl_2/ MeOH (9:1)], R_f = 0.10.

A2. 4-N-Tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine

41.7 g (86.4 mmol) of benzyl 1-[4-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine-1-carboxylate (starting material A9) in 1.0 l of methanol are hydrogenated over palladium/carbon (5%) for 4 h. The catalyst is filtered off and the solvent is removed, giving 30.3 g of the title compound as a colorless oil.

A3. 3-N-Tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine

13.77 g (28.5 mmol) of benzyl 4-[3-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]-piperazine-1-carboxylate (starting material A10) in 400 ml of methanol are hydrogenated over palladium/carbon (10%) for 4 h. The catalyst is filtered off and the solvent is removed, giving 10.35 g of the title compound as a solid oil.

General Procedure for starting materials A4-A6

N,N-carbonyldiimidazole (486 mg, 3.0 mmol) is added to a solution of 1,4-bis-(2-hydroxyethoxy)-2-butyne (187 mg, 1.0 mmol) in absolute CH_2Cl_2 (5 ml), and the mixture is stirred at RT for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (5 ml), the Boc-protected compound in question (A1 – A3, 2.2 mmol) is added and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further

purification is carried out by recrystallization using methanol/diethyl ether. The title compounds (A4 - A6) are obtained as colorless solids.

A4. **1,4-Bis-[4-(trans-4-N-*tert*-butoxycarbonylaminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-ethyl-2-oxy]-2-butyne**

MS: calc.: $C_{44}H_{72}N_6O_{12}$ (876.0), found: [MH^+] 877.0; [MNa^+] 945.3

A5. **1,4-Bis-[4-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne**

MS: calc.: $C_{46}H_{66}N_8O_{12}$ (922.1), found: [MH^+] 923.0; [MNa^+] 945.3

A6. **1,4-Bis-[4-(3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne**

MS: calc.: $C_{46}H_{66}N_8O_{12}$ (922.1), found: [MH^+] 923.0; [MNa^+] 945.3

A7. **1,6-Bis-[4-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne**

N,N-carbonyldiimidazole (660 mg, 4.08 mmol) is added to a solution of 2,4-hexadiyne-1,6-diol (150 mg, 1.36 mmol) in absolute CH_2Cl_2 (5 ml), and the mixture is stirred at room temperature for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (5 ml), 4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine (A2, 1.04 g, 3.0 mmol) is added and the mixture is stirred at room temperature overnight. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by recrystallization using methanol/diethyl ether. This gives the title compound (0.30 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.48.

MS: calc.: $C_{44}H_{58}N_8O_{10}$ (858.0), found: [MH^+] 858.9; [MNa^+] 881.2

A8. **Benzyl 4-{1-[trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexyl]carbonyl}piperazine-1-carboxylate**

HOBT (0.16 g, 1.2 mmol) is added to a solution of trans-4-(N-tert-butoxycarbonylaminomethyl)cyclohexanecarboxylic acid (0.40 g, 1.55 mmol) and benzyloxycarbonyl-1-

piperazine (0.34 g, 1.55 mmol) in absolute CH_2Cl_2 (9 ml) and Et_3N (0.96 ml), and the mixture is stirred at RT for 20 min. EDC (0.23 g, 1.2 mmol) is then added, and the mixture is stirred at RT overnight. The reaction solution is diluted with CH_2Cl_2 (15 ml) and extracted (2x) with semisaturated aqueous NH_4Cl solution (15 ml), dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification by chromatography [CH_2Cl_2/ MeOH (9:1)] over a silica gel column gives the title compound (0.71 g) as a colorless powder. TLC, silica gel, glass plates, [CH_2Cl_2/ MeOH (9:1)], R_f = 0.24.

A9. **Benzyl 4-[4-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine-1-carboxylate**

At 0°C, 25.0 g (106 mmol) of 4-(tert-butyloxycarbonylaminomethyl)benzylamine in 150 ml of dichloromethane are added dropwise to a solution of 22.4 g (111 mmol) of 4-nitrophenyl chloroformate in 200 ml of dichloromethane, and the mixture is stirred for 10 min. 15.6 ml (111 mmol) of triethylamine are then added dropwise, and the mixture is stirred at RT for 1.5 h. At 0°C, first 24.5 g (111 mmol) of benzyl piperazine-1-carboxylate in 80 ml of dichloromethane and then 15.6 ml (111 mmol) of triethylamine are then added dropwise. The mixture is stirred at RT for 16 h. The reaction mixture is then freed from the solvent and the crude product is chromatographed over silica gel (toluene/ethyl acetate = 1:1). Crystallization from diisopropyl ether gives 41.7 g of the title compound as a colorless solid of m.p. 108-112°C.

A10. **Benzyl 4-[3-(tert-butyloxycarbonylaminomethyl)benzylaminocarbonyl]piperazine-1-carboxylate**

At 0°C, 10.0 g (42.3 mmol) of 3-(tert-butyloxycarbonylaminomethyl)benzylamine in 200 ml of dichloromethane are added dropwise to a solution of 8.95 g (44.4 mmol) of 4-nitrophenyl chloroformate in 200 ml of dichloromethane, and the mixture is stirred for 60 min. 6.2 g (44.4 mmol) of triethylamine in 50 ml of dichloromethane are then added dropwise, and the mixture is stirred at RT for 1.5 h. At 0°C, first 9.8 g (44.4 mmol) of benzyl piperazine-1-carboxylate in 100 ml of dichloromethane and then 6.2 g (44.4 mmol) of triethylamine in 50 ml of dichloromethane are then added dropwise. The mixture is stirred at RT for 16 h. The reaction mixture is then freed from the solvent and the crude product is chromatographed over silica gel (toluene/ethyl acetate = 1:1), giving 13.77 g of the title compound as a colorless solid of m.p. 128°C.

A11. **1,12-Bis-[4-(4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne**

N,N-carbonyldiimidazole (370 mg, 2.31 mmol) is added to a solution of 5,7-dodecadiyne-1,12-diol (150 mg, 0.77 mmol) in absolute CH_2Cl_2 (4 ml), and the mixture is stirred at room temperature for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (4 ml), 4-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine (A2, 590 mg, 1.70 mmol) is added and the mixture is stirred at room temperature overnight. The reaction solution is diluted with CH_2Cl_2 (4 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by recrystallization using methanol/diethyl ether. This gives the title compound (0.39 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.71.

MS: calc.: $C_{50}H_{70}N_8O_{10}$ (942.0), found: [MH^+] 943.1; [MNa^+] 965.3

A12. **1,12-Bis-[4-(3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne**

N,N-carbonyldiimidazole (370 mg, 2.31 mmol) is added to a solution of 5,7-dodecadiyne-1,12-diol (150 mg, 0.77 mmol) in absolute CH_2Cl_2 (4 ml), and the mixture is stirred at room temperature for 0.5 h. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (4 ml), 3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine (A3, 590 mg, 1.70 mmol) is added and the mixture is stirred at room temperature overnight. The reaction solution is diluted with CH_2Cl_2 (4 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by recrystallization using methanol/diethyl ether. This gives the title compound (0.37 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.68.

MS: calc.: $C_{50}H_{70}N_8O_{10}$ (942.0), found: [MH^+] 943.1; [MNa^+] 965.3

A13. **1,6-Bis-[4-(3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne**

N,N-carbonyldiimidazole (660 mg, 4.08 mmol) is added to a solution of 2,4-hexadiyne-1,6-diol (150 mg, 1.36 mmol) in absolute CH_2Cl_2 (5 ml), and the mixture is stirred at room temperature for

0.5 h. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. The resulting residue is taken up in absolute CH_2Cl_2 (5 ml), 3-N-tert-butoxycarbonylaminomethylbenzylaminocarbonyl-1-piperazine (A3, 1.04 g, 3.0 mmol) is added and the mixture is stirred at room temperature overnight. The reaction solution is diluted with CH_2Cl_2 (5 ml) and extracted with a semisaturated aqueous NaCl solution (10 ml). The organic phase is dried over $MgSO_4$, filtered off and concentrated under reduced pressure. Further purification is carried out by recrystallization using methanol/diethyl ether. This gives the title compound (0.47 g) as a colorless solid. TLC, silica gel (glass plates), [toluene/acetone (7:3)], R_f = 0.47.

MS: calc.: $C_{44}H_{58}N_8O_{10}$ (858.0), found: [MH^+] 858.9; [MNa^+] 881.2

Commercial utility

As tryptase inhibitors, the compounds according to the invention have useful pharmacological properties which make them commercially utilizable. Human tryptase is a serin protease which is the main protein in human mast cells. Tryptase comprises eight closely related enzymes (α1, α2, β1a, β1b, β2, β3, mMCP-7-like-1, mMCP-7-like-2; 85 to 99% sequence identity) (cf. Miller et al., J. Clin. Invest. 84 (1989) 1188-1195; Miller et al., J. Clin. Invest. 86 (1990) 864-870; Vanderslice et al., Proc. Natl. Acad. Sci., USA 87 (1990) 3811-3815; Pallaoro et al., J. Biol. Chem. 274 (1999) 3355-3362). However, only the β-tryptases (Schwartz et al., J. Clin. Invest. 96 (1995) 2702-2710; Sakai et al., J. Clin. Invest. 97 (1996) 988-995) are activated intracellularly and stored in catalytically active form in secretory granules. Compared with other known serin proteases, such as, for example, trypsin or chymotrypsin, tryptase has some special properties (Schwartz et al., Methods Enzymol. 244, (1994), 88-100; G. H. Caughey, "Mast cell proteases in immunology and biology". Marcel Dekker, Inc., New York, 1995). Tryptase from human tissue has a noncovalently-linked tetrameric structure which has to be stabilized by heparin or other proteoglycanes to be proteolytically active. Together with other inflammatory mediators, such as, for example, histamine and proteoglycanes, tryptase is released when human mast cells are activated. Because of this, tryptase is thought to play a role in a number of disorders, in particular in allergic and inflammatory disorders, firstly because of the importance of the mast cells in such disorders and secondly since an increased tryptase concentration was observed in a number of disorders of this type. Thus, tryptase is associated, inter alia, with the following diseases: acute and chronic (in particular inflammatory and allergen-induced) airway disorders of various origins (for example bronchitis, allergic bronchitis, bronchial asthma, COPD); interstitial lung disorders; disorders based on allergic reactions of the upper airways, (pharynx, nose) and the adjacent regions (for example paranasal sinuses, conjunctivae), such as, for example allergic conjunctivitis and allergic rhinitis; disorders of the arthritis type (for example rheumatoid arthritis); autoimmune disorders, such as multiple sclerosis; furthermore periodontitis, anaphylaxis, interstitial cystitis, dermatitis, psoriasis, sclerodermia/systemic sclerosis, inflammatory intestinal disorders (Crohn's disease, inflammatory bowel disease) and others. In particular, tryptase seems to be connected directly to the pathogenesis of asthma (Caughey, Am. J. Respir. Cell Mol. Biol. 16 (1997), 621-628; R. Tanaka, "The role of tryptase in allergic inflammation" in: Protease Inhibitors, IBC Library Series, 1979, Chapter 3.3.1-3.3.23).

A further subject of the invention relates to the compounds according to the invention for use in the treatment and/or prophylaxis of diseases, in particular the diseases mentioned.

The invention likewise relates to the use of the compounds according to the invention for preparing medicaments which are employed for the treatment and/or prophylaxis of the diseases mentioned.

Medicaments for the treatment and/or prophylaxis of the diseases mentioned, which contain one or more of the compounds according to the invention, are furthermore a subject of the invention.

The medicaments are prepared by processes which are known per se and familiar to the person skilled in the art. As medicaments, the compounds according to the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical excipients, for example in the form of tablets, coated tablets, capsules, suppositories, patches, emulsions, suspension, gels or solutions, the active compound content advantageously being between 0.1 and 95%.

The person skilled in the art is familiar on the basis of his/her expert knowledge with the excipients which are suitable for the desired pharmaceutical formulations. In addition to solvents, gel-forming agents, ointment bases and other active compound vehicles, it is possible to use, for example, antioxidants, dispersants, emulsifiers, preservatives, solubilizers or permeation promoters.

For the treatment of disorders of the respiratory tract, the compounds according to the invention are preferably also administered by inhalation. For this purpose, they are either administered directly as a powder (preferably in micronized form) or by nebulization of solutions or suspensions which contain them. With respect to the preparations and administration forms, reference is made, for example, to the details in European Patent 163 965.

For the treatment of dermatoses, the compounds according to the invention are in particular used in the form of those medicaments which are suitable for topical administration. For the preparation of the medicaments, the compounds according to the invention (= active compounds) are preferably mixed with suitable pharmaceutical excipients and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations which may be mentioned are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The medicaments according to the invention are prepared by processes known per se. The dosage of the active compounds in the case of systemic therapy (p.o. or i.v.) is between 0.1 and 10 mg per kilogram per day.

Biological investigations

The documented pathophysiological effects of mast cell tryptase are caused directly by the enzymatic activity of the protease. Accordingly, they are reduced or blocked by inhibitors which inhibit the enzymatic activity of the tryptase. A suitable measure for the affinity of a reversible inhibitor to the target protease is the equilibrium dissociation constant K_i of the enzyme-inhibitor complex. This K_i value can be determined via the effect of the inhibitor on the tryptase-induced cleavage of a chromogenic peptide-p-nitroanilide substrate or a fluorogenic peptide-aminomethylcoumarin substrate.

Methodology

The dissociation constants for the tryptase-inhibitor complexes are determined under equilibrium conditions in accordance with the general proposals of Bieth (Bieth JG, Pathophysiological Interpretation of kinetic constants of protease inhibitors, Bull. Europ. Physiopath. Resp. 16:183-195, 1980) and the methods of Sommerhoff et al. (Sommerhoff CP et al., A Kazal-type inhibitor of human mast cell tryptase: Isolation from the medical leech Hirudo medicinalis, characterization, and sequence analysis, Biol. Chem. Hoppe-Seyler 375: 685-694, 1994).

Human tryptase is isolated from lung tissue or prepared recombinantly; the specific activity of the protease, determined by titration, is usually greater than 85% of the theoretical value. In the presence of heparin (0.1-50 µg/ml) for stabilizing the protease, constant amounts of the tryptase are incubated with increasing amounts of the inhibitors. After an equilibrium between the reaction partners has formed, the remaining enzyme activity after addition of the peptide-p-nitroanilide substrate tos-Gly-Pro-arg-pNA is determined and the cleavage of the latter is monitored at 405 nm for 3 min. Alternatively, the remaining enzymatic activity can also be determined using fluorogenic substrates. The apparent dissociation constants K_{iapp} (i.e. in the presence of substrate) are subsequently determined by adapting the enzyme rates to the general equation for reversible inhibitors (Morrison JF, Kinetics of the reversible inhibition of enzyme-catalyzed reactions by tight-binding inhibitors, Biochim. Biophys. Acta 185, 269-286, 1969) using non-linear regression:

$$V_i/V_0 = 1 - \{E_t+I_t+K_{iapp}-[(E_t+I_t+K_{iapp})^2-4E_tI_t]^{1/2}\}/2E_t$$

V_i and V_0 are the rates in the presence and absence, respectively, of the inhibitor, and E_t and I_t are the tryptase and inhibitor concentrations, respectively.

The apparent dissociation constants determined for the compounds according to the invention are shown in Table A below, where the numbers of the compounds correspond to the numbers of the compounds in the examples.

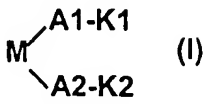
Table A

Inhibition of human tryptase

Compound	K_{iapp} (μM)
1	0.086
2	0.00035
3	0.008
4	0.00025
5	0.012
6	0.0014
7	0.008

Patent Claims

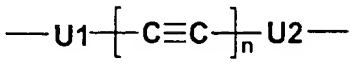
1. Compounds of the formula I



(I)

in which

M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [$-CH_2-$], ethylene [$-CH_2-CH_2-$], trimethylene [$-CH_2-CH_2-CH_2-$], tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$] or isopropylidene [$-C(CH_3)_2-$],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -C(O)-, -O-C(O)-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH-, -O-C(O)-O-, $-O-(CH_2)_r-C(O)-$, $-O-(CH_2)_m-O-C(O)-$ or $-O-(CH_2)_m-NH-C(O)-$,

r is 1, 2, 3 or 4,

m is 1, 2, 3 or 4,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH- or -O-C(O)-O-,

B1 and B2 are identical or different and are 1-4C-alkylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,4-phenylene, 1,3-phenylene, 1,4-piperazinylene or 1,4-piperidinylene,

K1 is -B3-X1, -B3-Y1 or -B3-Z1-B5-X1,

K2 is -B4-X2, -B4-Y2 or -B4-Z2-B6-X2,

B3 and B4 are identical or different and are a bond or 1-4C-alkylene,

B5 and B6 are identical or different and are a bond or 1-2C-alkylene,

X1 and X2 are identical or different and are amino, aminocarbonyl or amidino,

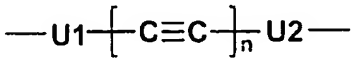
Y1 and Y2 are imidazol-1-yl,

Z1 and Z2 are identical or different and are 5,2-pyridinylene, 6-methyl-5,2-pyridinylene, 4,1-piperidinylene, 3,6-indazolylene, 3,6-indolylene, 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, the salts of these compounds, and the N-oxides of the nitrogen-containing heteroaryls, heteroarylenes and heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to

the meaning of the variables A3, A4, A5, A6, B1, B2, B3, B4, Z1, Z2, X1 or X2, there would be a direct linkage of two heteroatoms.

2. Compounds of the formula I according to claim 1 in which
M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [$-CH_2-$], ethylene [$-CH_2-CH_2-$], trimethylene [$-CH_2-CH_2-CH_2-$], tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$] or isopropylidene [$-C(CH_3)_2-$],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -O-C(O)-, -NH-C(O)-, -O-C(O)-NH-, -NH-C(O)-O-, -NH-C(O)-NH-, -O-C(O)-O-, $-O-(CH_2)_r-C(O)-$, $-O-(CH_2)_m-O-C(O)-$ or $-O-(CH_2)_m-NH-C(O)-$,

r is 1 or 2,

m is 2,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,

B1 and B2 are identical or different and are 1-4C-alkylene, 1,4-cyclohexylene, 1,3-cyclohexylene, 1,4-phenylene, 1,3-phenylene, 1,4-piperazinylene or 1,4-piperidinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical or different and are a bond or 1-2C-alkylene,

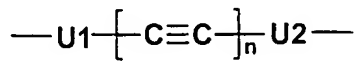
B5 and B6 are identical or different and are a bond or 1-2C-alkylene,

X1 and X2 are identical or different and are amino or amidino,

Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene, 1,3-cyclohexylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

3. Compounds of the formula I according to claim 1 in which
M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [-CH_2-], tetramethylene [-CH_2-CH_2-CH_2-CH_2-] or isopropylidene [-$C(CH_3)_2$-],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -O-C(O)-, -O-C(O)-NH- or -O-$(CH_2)_m$-O-C(O)-,

m is 2,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,

B1 and B2 are identical or different and are ethylene or 1,4-piperazinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical or different and are a bond or methylene,

B5 and B6 are identical and are methylene,

X1 and X2 are identical and are amino,

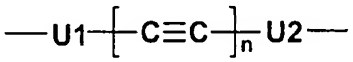
Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present,

and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

4. Compounds of the formula I according to claim 1 in which

M is a central building block of the formula below



n is 1 or 2,

U1 and U2 are identical or different and are methylene [-CH_2-] or isopropylidene [-$C(CH_3)_2$-],

A1 is -A3-B1-A5-,

A2 is -A4-B2-A6-,

A3 and A4 are identical or different and are -O-C(O)-, -O-C(O)-NH- or -O-$(CH_2)_m$-O-C(O)-,

m is 2,

A5 and A6 are identical or different and are -C(O)-, -C(O)-NH- or -NH-C(O)-,

B1 and B2 are identical or different and are ethylene or 1,4-piperazinylene,

K1 is -B3-Z1-B5-X1,

K2 is -B4-Z2-B6-X2,

B3 and B4 are identical and are a bond or methylene,

B5 and B6 are identical and are methylene,

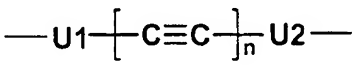
X1 and X2 are identical and are amino,

Z1 and Z2 are identical or different and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,

and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present,

and the salts of these compounds, and the N-oxides of the nitrogen-containing heterocycloalkylenes, and their salts, where all those compounds are excluded in which, owing to the meaning of the variables A3, A4, A5, A6, B1 or B2, there would be a direct linkage of two heteroatoms.

5. Compounds of the formula I according to claim 1 in which
M is a central building block of the formula below



n is 1 or 2,
U1 and U2 are identical and are methylene [$-CH_2-$]
or tetramethylene [$-CH_2-CH_2-CH_2-CH_2-$],
A1 is -A3-B1-A5-,
A2 is -A4-B2-A6-,
A3 and A4 are identical and are -O-C(O)- or $-O-(CH_2)_m-O-C(O)-$,
m is 2,
A5 and A6 are identical and are -C(O)- or -C(O)-NH-,
B1 and B2 are identical and are 1,4-piperazinylene,
K1 is -B3-Z1-B5-X1,
K2 is -B4-Z2-B6-X2,
B3 and B4 are identical and are a bond or methylene,
B5 and B6 are identical and are methylene,
X1 and X2 are identical and are amino,
Z1 and Z2 are identical and are 1,3-phenylene, 1,4-phenylene or 1,4-cyclohexylene,
and where on the direct route between the terminal nitrogen atoms 20 to 45 bonds have to be present, and the salts of these compounds.

6. Compounds of the formula I according to claim 1 with the chemical designation
1,4-bis-[4-(trans-4-aminomethylcyclohexylcarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,4-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,4-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxyethyl-2-oxy]-2-butyne,
1,6-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne,
1,12-bis-[4-(4-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne,
1,12-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-5,7-dodecadiyne, and
1,6-bis-[4-(3-aminomethylbenzylaminocarbonyl)-1-piperazinylcarbonyl-1-oxy]-2,4-hexadiyne,
and the salts of these compounds.

7. Compounds of the formula I according to claim 1 for the treatment of diseases.

8. A medicament comprising one or more compounds of the formula I according to claim 1 together with customary pharmaceutical auxiliaries and/or excipients.

9. Use of compounds of the formula I according to claim 1 for the production of medicaments for the treatment of airway disorders.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 00/12838

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D295/205 A61K31/495 A61P29/00 A61P11/06 A61P27/14 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 24395 A (ARRAY BIOPHARMA, INC.) 20 May 1999 (1999-05-20) cited in the application page 7, line 5 -page 15, line 31 ---	1-9
A	WO 98 04537 A (ARRIS PHARMACEUTICAL CORPORATION) 5 February 1998 (1998-02-05) cited in the application page 3, line 10 -page 19, line 5 ---	1-9
A	WO 96 09297 A (ARRIS PHARMACEUTICAL CORPORATION) 28 March 1996 (1996-03-28) cited in the application page 5, line 4 -page 17, line 19 --- -/--	1-9

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
21 March 2001	09.04.01

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Kyriakakou, G

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 95 32945 A (ARRIS PHARMACEUTICAL CORPORATION) 7 December 1995 (1995-12-07) cited in the application page 4, line 26 -page 15, line 10 ---	1-9
A	G. H. CAUGHEY ET AL.: "bis(5_Amidino-2-Benzimidazolyl)methane and related Amidines are potent, reversible Inhibitors of mast cell Tryptases" THE JOURNAL OF PHARMACOLOGY ANDEXPERIMENTAL THERAPEUTICS, vol. U.264, no. 2, 1993, pages 676-682, XP002064911 U. S. A the whole document ---	1-9
A	KENNETH D. RICE ET AL.: "inhibitors of tryptase for the treatment of Mast Cell-mediated Diseases" CURRENT PHARMACEUTICAL DESIGN 1998,4,381-396, vol. 4, no. 5, 1998, pages 381-396, XP002108322 the whole document ---	1-9
A	JÖRG STÜRZEBECHER ET AL.: "inhibition of Human Mast cell Tryptase by Benzamidine Derivatives" BIOL. CHEM. HOPPE-SEYLER, vol. 373, 1992, pages 1025-1030, XP002103558 berlin the whole document ---	1-9
A	SHIN'ICHIO ONO ET AL.: "syntheses and Evaluation of Amidinobenzofuran Derivatives as tryptase Inhibitors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, no. 9, 1999, pages 3285-3290, XP004183725 the whole document ---	1-9
A	MARCEL BERTAULT ET AL.: "Synthesis and Solid-state Polymerization Properties of Symmetrical and Unsymmetrical Diacetylene Derivatives containing a 'Polymerogenic' Side Group" J. CHEM. SOC., CHEM. COMMUN., 1988, pages 163-166, XP002139152 the whole document -----	1-6

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 00/12838

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1-5,7-9
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1-5,7-9

Present claims 1-5, 7-9 relate to an extremely large number of possible compounds/compositions. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds/compositions claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the those compounds etc. prepared in the examples and closely related homologous compounds.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. ..onal Application No
PCT/EP 00/12838

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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